

REMARKS

Applicants are in receipt of the Office Action mailed June 9, 2008. Following careful study of this Office Action, Applicants have the following remarks.

Telephonic Interview

The undersigned expresses his appreciation to Examiner Zeman for his willingness to briefly discuss the outstanding new matter rejection in this case in a telephonic interview held September 8, 2008. Although no accord was reached, Applicants appreciate the opportunity to better understand the Examiner's position and to address his objections to the claims.

The Applicants have now included newly cited references to support for the claim limitations beyond those discussed with the Examiner in the interview.

Claim Rejections

I. Rejection of claims 31-32 and 34-45 pursuant to 35 U.S.C. 112(1).

The Examiner has indicated his belief that claims 31-32 and 34-45 violate the written description requirement because among the Clostridial toxins of the present specification, only the TeTx dichains of Example 6 are allegedly described as having an activity of 3.3×10^5 LD₅₀/mg or greater.

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Applicants respectfully disagree, incorporate by reference the arguments advanced in the Amendment and Reply filed November 23, 2007, and have the following additional remarks.

Applicants respectfully believe that the Examiner has mistakenly misunderstood the phrase alleged to be new matter: "wherein the active neurotoxin possesses mouse lethality of 3.3×10^5 LD₅₀/mg or greater" This phrase defines the word "active", and finds basis in the specification as filed.

The Examiner does not dispute that the present specification is replete with description of "active" Clostridial neurotoxins; *see, e.g.*, page 3 line 15-30, in which an "active Clostridial neurotoxin" can be "any of a variety of such toxins", including tetanus toxin, botulinum toxin A, botulinum toxin B, botulinum toxin C, botulinum toxin D, botulinum toxin E, botulinum toxin F, and botulinum toxin G.

The specification as filed also states that in Clostridial neurotoxins generally, including tetanus toxin, botulinum toxin A, botulinum toxin B, botulinum toxin C, botulinum toxin D, botulinum toxin E, botulinum toxin F, and botulinum toxin G, "can be inactivated by an amino acid change in its light chain." *Specification*, Page 3, lines 20-26(emphasis added).

Therefore, it cannot reasonably be disputed that the Specification describes both:

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- a) that the concept of "active" described in the Specification is a common characteristic and its definition is irrespective of the type of Clostridial neurotoxin one is discussing, and
- b) that the activity of each of: tetanus toxin, botulinum toxin A, botulinum toxin B, botulinum toxin C, botulinum toxin D, botulinum toxin E, botulinum toxin F, and botulinum toxin G is conferred by the light chain.

It is equally clear that the Specification discloses that for both TeTX and BoNT toxins A-G, the light (L) chain of each toxin is a protease responsible for blocking neurotransmitter release through cleavage of a cellular protein. See e.g., Specification page 2, lines 9-16, (disclosing that the L chain of TeTX and BoNT is responsible for blocking neurotransmitter release); page 2, 17-21 (describing that TeTX is toxic by virtue of cleaving VAMP and thus preventing docking of the neurotransmitter vesicle with the presynaptic membrane); and page 2, 22-32 (in which the Specification describes that the BoNT neurotoxins cleave VAMP or other targets involved in neurotransmitter release).

It is therefore clear that since the L chain confers the toxic activity, any Clostridial neurotoxin in which the toxic activity is no greater than that activity conferred by the H chain alone must be considered inactive. Moreover, it follows (and would certainly be apparent to a person of ordinary skill in the art) that since the L chain of TeTX and BoNT

confers toxic activity, the H chains alone of TeTX and BoNT, respectively are equally inactive.

In a mouse lethality assay, the activity of TeTX H chain alone ($<50 \text{ LD}_{50}/\text{mg}$) was essentially the same as that of native H chain and the Ala²³⁴-LC; see Specification at page 25, lines 1-16. This result ($<50 \text{ LD}_{50}/\text{mg}$) is characterized at page 25, line 21 as the "absence of activity" in this assay format. T

A similar experiment (Example 20, page 39) was done using reconstituted BoNT light and heavy chains, and toxicity of the dichain material containing recombinant L (both mutated and unmutated) and H chains was assessed using the mouse lethality assay. "Active" reconstituted BoNT dichain toxins had a mouse lethality of 6×10^7 and $7 \times 10^7 \text{ LD}_{50}/\text{mg}$, whereas mice injected with a dichain containing a mutant Tyr²²⁷ L chain showed no signs of botulism, and were therefore considered "inactive". *Id.* at line 19.

As a result, the definition of the term "active" ($3.3 \times 10^5 \text{ LD}_{50}/\text{mg}$ or greater) contained in e.g., claim 31 is fully and adequately described as required by 35 USC §112(1) in the specification. Table 2 describes active Clostridial neurotoxin (TeTx) having an activity of $3.3 \times 10^5 \text{ LD}_{50}/\text{mg}$ or greater ($3.3 \times 10^5 \text{ LD}_{50}/\text{mg}$ and $0.5 \times 10^3 \text{ LD}_{50}/\text{mg}$). Example 20 at page 39 describes active Clostridial toxins (BoNT) having a mouse lethality of $3.3 \times 10^5 \text{ LD}_{50}/\text{mg}$ or greater ($6 \times 10^7 \text{ LD}_{50}/\text{mg}$ and $7 \times 10^7 \text{ LD}_{50}/\text{mg}$). Furthermore, Example 23 describes a non-naturally occurring tri-chain preparation containing BoNT L

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chain, BoNT H chain, and TeTx L chain, which "produced symptoms of botulism both *in vitro* and *in vivo*" and "gave a mouse toxicity of $>107 \text{ LD}_{50}/\text{mg}$ ". *Specification*, page 43, lines 8-11. Therefore, all of these examples of active Clostridial neurotoxins have a mouse lethality of $3.3 \times 10^5 \text{ LD}_{50}/\text{mg}$ or greater.

As stated in the Amendment of November 23, 2008, far from requiring word-for-word disclosure in the specification, written description law indicates "drawings alone may provide a 'written description' of an invention as required by 35 USC 112". PTO FINAL EXAMINER GUIDELINES ON WRITTEN DESCRIPTION REQUIREMENT, 66 Fed. Reg. 1099, 1106 and note 39 (December 29, 2000) (hereinafter the "PTO EXAMINER GUIDELINES"), citing *Vas-Cath v. Mahurkar*, 935 F.2d 1555, 19 USPQ2d 1111 (Fed. Cir. 1991). Additionally, the written description requirement may be satisfied by using such non-verbal descriptive means as structures, figures, diagrams, formulas, indeed "it is now well accepted that a satisfactory description may be in the claims or any other portion", or combination of portions, of the originally filed specification. PTO EXAMINER GUIDELINES at note 4. Obviously data contained in the application as filed is also extremely germane in determining whether a person of ordinary skill in the relevant art would perceive the Applicants have invented the claimed subject matter.

Thus, the person of ordinary skill in the art would clearly understand from reading the present specification that the inventors of the presently claimed invention invented a

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composition comprising an active Clostridal neurotoxin
("active being defined as having mouse lethality of 3.3×10^5
LD₅₀/mg or greater) joined to a neuropharmacological agent
wherein the toxin binds a target host cell and cleaves SNAP-
25, VAMP and cellubrevin.

For these reasons the Applicants respectfully request that
the Examiner reconsider the present rejection and permit the
pending claims to proceed to issue.

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CONCLUSION

No fee is thought to be due in connection with the present response, since this response is being filed within or before the end of the three-month shortened statutory period. However, if Applicants are in error in this regard kindly use Deposit Account 50-4004 for the payment of any other any charge now due, or to credit any overpayment.

Respectfully submitted,

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